Hormone Replacement 2004: Evidence and Alternatives

Mary V. Krueger DO, MPH
MAJ, MC, USA
Family Health Center
Dewitt Army Community Hospital

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The Mystique of Menopause

- Andy Rooney:

  "As I grow in age, I value older women most of all."

  Reason #1: An older woman will never wake you in the middle of the night to ask:

  "What are you thinking?"

  She doesn't care what you think

Objectives

- After this session participants will be able to:
  - Discuss the evidence on HRT
  - Understand current recommendations for HRT use for menopausal conditions
  - Advise their patients on HRT and its alternatives for menopausal conditions

Outline

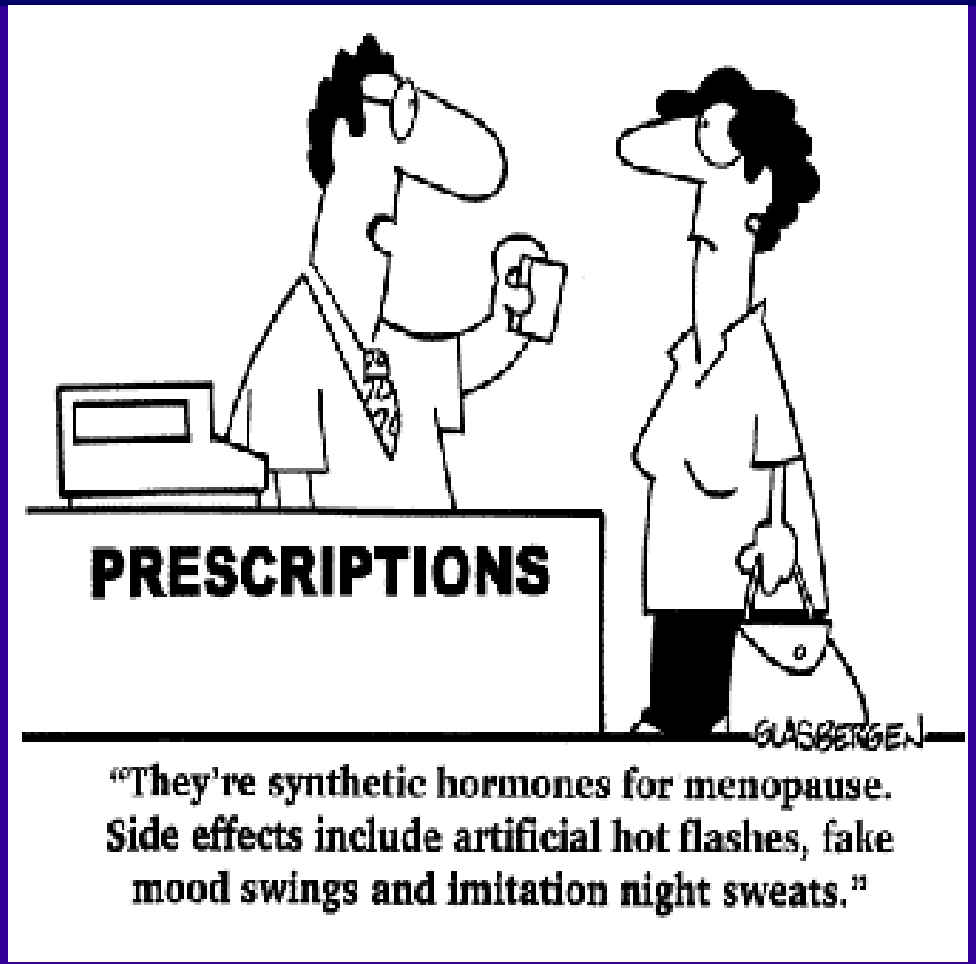
- History of hormone replacement (HRT)
- Menopause: What and Who?
- Summary of the evidence
- Recommendations for HRT use
- Alternatives to HRT
- Conclusions

History

- 1940: DES used for “healthy pregnancy”
- 1966: *Feminine Forever* published by Dr. Wilson
- 1976: Unopposed estrogen linked to endometrial cancer
- 1980s: Estrogen and Progestin given
- 2002: WHI report made the news and remained there

Who are we treating?

- 4000 women enter menopause daily
- Well-educated, participate in their care
- May favor “non-traditional” alternatives



How are we treating?

- Pills
  - Many varieties of estrogens and progestins
- Transdermal patches
  - Vivelle and Menorest
- Gels
- Vaginal rings
  - Estring 2mg; change Q 3 months
- Vaginal creams

Should We be Treating?

- Question raised both by science and society: medication versus celebration

"If we are to be well, we must care for ourselves. We must not cast the old woman out, but become her more abundantly."

-Germaine Greer, *The Change*

What Are We Treating?

- Menopause:
  - Cessation of menstrual flow for 12 consecutive months in the absence of confounding factors
  - Average age of onset: 51 years 4 months
  - Lab confirmation: FSH>40, Estradiol <30
  - 90% of women are post-menopausal by 55

What are We Really Treating?

- Perimenopause:
  - May be 4 years prior to cessation of menses and can last 2 – 7 years
  - Associated symptoms have often lead to HRT initiation
  - Five million women currently on HRT but this number is decreasing

Vasomotor Symptoms

Vasomotor Symptoms

- Occur in 60 - 80%
- Severe in 15%
- Worse in iatrogenic menopause
- Primary reason for starting or restarting HRT
- Primary SE of stopping HRT

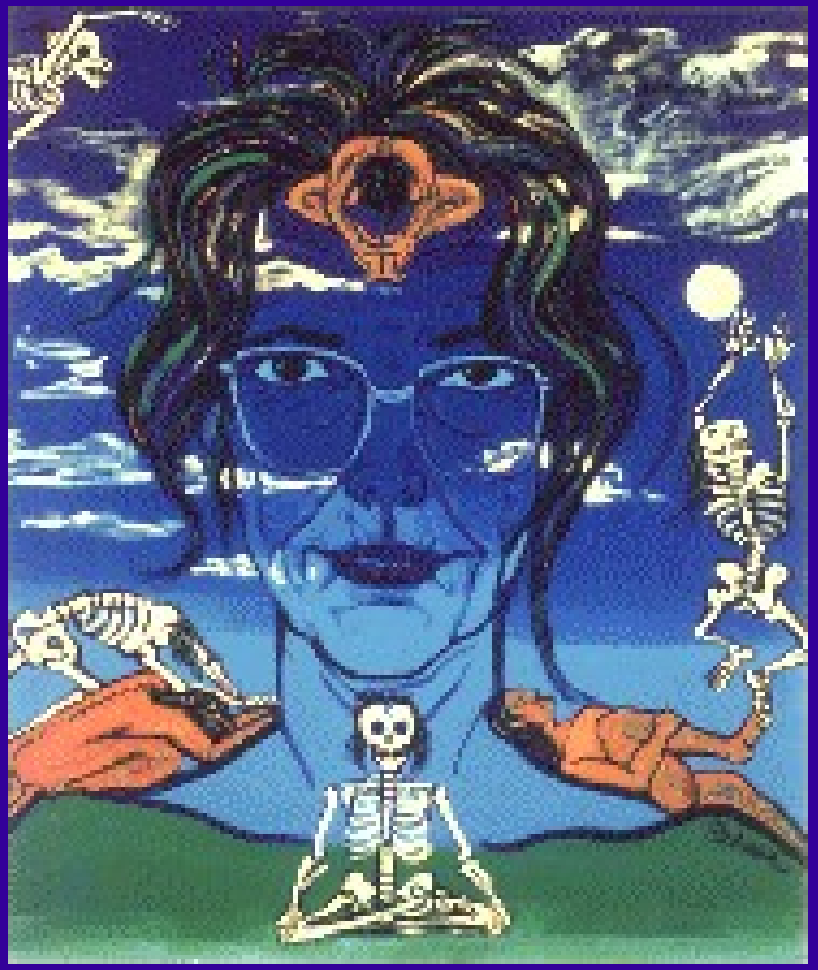
Mood Swings

- Multifactorial: Stress, empty nesters, fatigue
- The gamut of tears, laughter, depression
- Estrogen/ Serotonin receptor association
- Often reported by significant others

Dementia/ Memory Loss

Genitourinary Atrophy

- Vaginal dryness and burning
- Thinned mucosa
- May complain of pain with intercourse
- Increased microhematuria



Cardiovascular Disease

- After menopause, cardiac risk approaches that of men
- Cardiac disease is #1 killer of women
- LDL increases
- HDL decreases
- Triglycerides increase

Lipoproteins in Menopause

No of patients	Total Chol	LDL-C	HDL-C	Triglycerides
541	⇑			
170				
394		ND		
542				

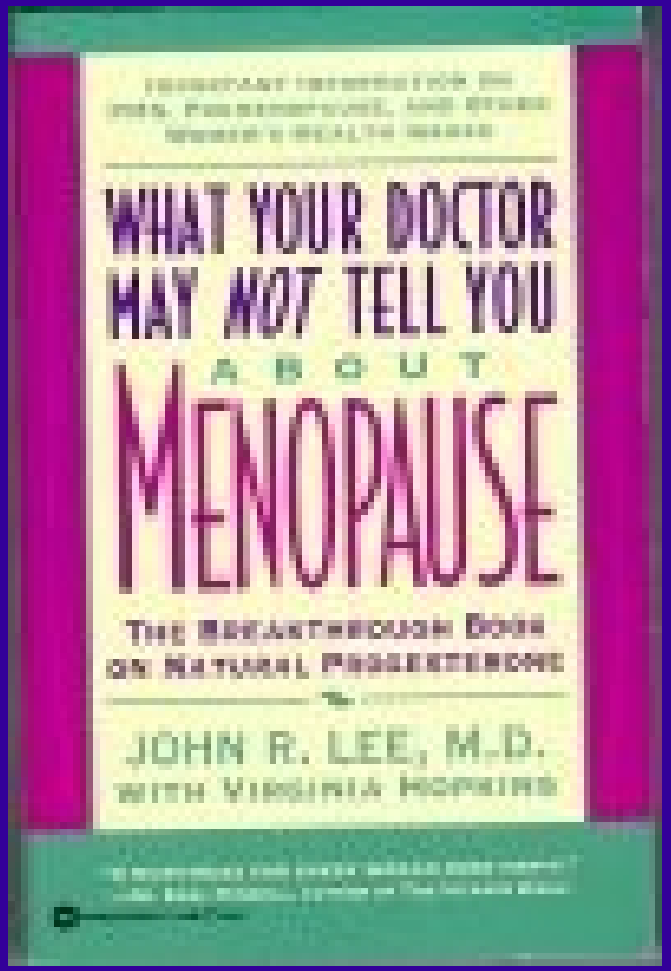
NEJM 1989;321:641
Q J Med 1992;85:307

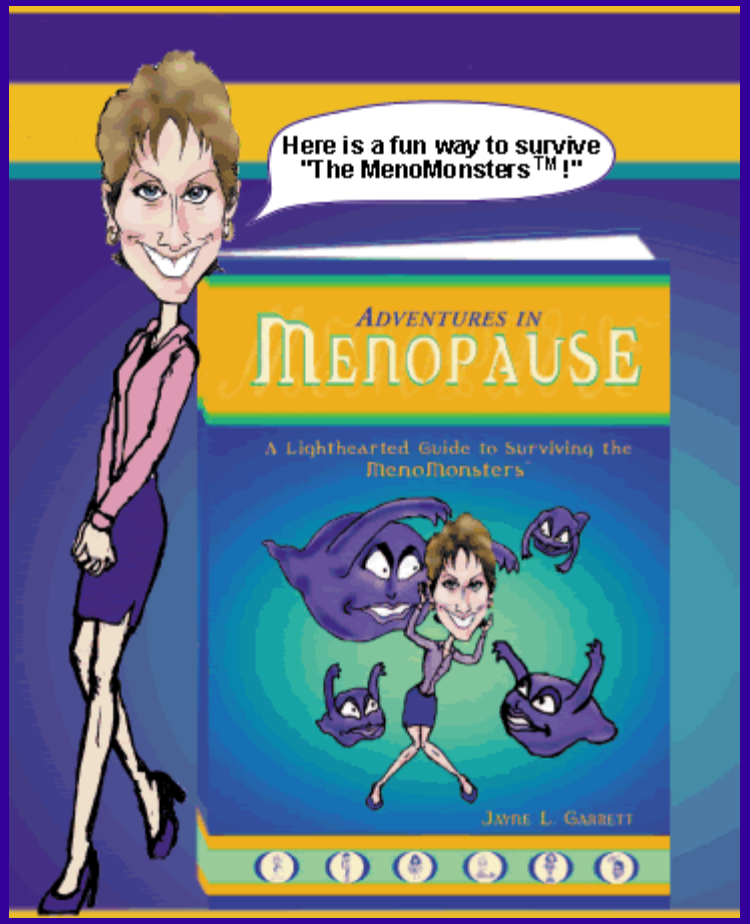
Maturitas 1990;21:321
Atheroscl 1993;98:83

Osteoporosis

- T score $\geq$ 2.5 SD below young adults
- 10 million Americans
- 1.5 million fractures annually
- Hip fractures
  - 1 out of 6 women
  - 1/2 can not walk without assist
  - 1/4 die within one year of fracture

Where do Our Patients get Their Evidence?





The Evidence

- Pre-HERS
  - Nurses Health Study
  - PEPI
- HT and Secondary Prevention
  - HERS I and II
  - PHASE
  - ERA
- HT and Primary Prevention
  - WHI

Nurses Health Study

- 121,000 nurses, 30 – 55 years old, surveyed every 2 years
- Assessed multiple risk factors for disease
- **Outcomes**
  - HRT protective for primary heart disease
  - Increase in CHD for HRT use > one year

PEPI trial

- Followed 875, postmenopausal, healthy women for 3 years
- Tested effect of various hormone regimens on markers for CHD and osteoporosis
- **Outcomes**:
  - Increased HDL, decreased LDL
  - Increased bone density

HERS I & II

- Enrolled 2,763 postmenopausal women with CVD (Secondary prevention)
- Tested whether HRT would prevent second event in women with CVD
- Outcomes
  - Increased MI in 1st year, decrease at year 4 and leveled off by 6.8 years
  - Women on Estrogen who suffer MI are less likely to die from their CHD

ERA trial

- Enrolled 302 women, average age of 65, with known CAD, assigned to E, E+P or placebo and followed 3.2 years
- Tested effect of regimen on coronary plaque progression
- **Outcome**: No difference in progression of lesions

PHASE

- Notable for use of transdermal estrogen, avoiding 1st pass effect
- Followed for 4 years
- Endpoints: death, AMI or any CAD hospitalization
- Outcomes: Transdermal HRT showed 23% higher endpoint rate than placebo

Mystique of Menopause II

"Older women are dignified. They seldom have a screaming match with you at the opera or in the middle of an expensive restaurant. Of course, if you deserve it, they won't hesitate to shoot you if they think they can get away with it."

-Andy Rooney

WHI Overview

- Largest study of its kind undertaken
- 161,000 women enrolled
- Clinical trials began in 1991
  - E+P arm 16,608
  - E only arm 10,739
- Stopped 2 years early
  - E+P arm stopped 9 July 2002
  - Estrogen only arm stopped 2 March 2004

WHI Participants

- Age: 50 – 79; average age 63.3
  - 10% in the 50 – 59 year old age group
  - 25% in the 70 -79 year old age group
- Hypertension: 36%
- BMI >30: 34%
- Current or former smokers: 49%

WHI Objectives

- Assess long term outcomes of HRT on:
  - Cardiovascular disease**
  - Breast**, colon, and endometrial cancer
  - Hip fracture**
  - Memory loss
  - DVT/PE
- Not designed to assess short-term effects of therapy for vasomotor sx

WHI E+P: Cancer

- Total: 52.9/10,000 E+P vs 52.3/10,000
- Breast Cancer: Increase in E+P arm reason for stopping trial
  - Not statistically significant, but exceeded preset threshold by DSMB
- Colon Cancer: Decrease in E+P arm
- Endometrial Cancer: No difference

WHI E+P: Cardiovascular

- CAD: Overall 29% higher rate in E+P
  - Equal number of revascularization procedures and cardiac deaths
  - Excess events in non-fatal MI group
- Stroke:
  - Equal number of fatal strokes
- DVT/PE:
  - 10 x number reported by USPSTF

Creasman: AM J Obs Gyn, Sept 03 Miller etal: Ann Int Med, 2002

WHI E+P: Fractures

- Hip fractures reduced by 34%
- Vertebral fractures reduced
  - Only 40% symptomatic
  - No routine radiographs to screen for vertebral fractues
- Patients with osteoporosis excluded from enrollment

WHI Estrogen Only

- Enrolled 10,739 women, aged 50 -79, and treated with estrogen or placebo
- Average follow-up of 6.8 years
- Tested primary prevention/safety estrogen
- Outcomes:
  - Increased risk in stroke, decreased hip fx
  - No change in breast CA, CAD, colon CA

WHIMS E+P

- Enrolled 4500 women 65 – 79
- Participants memory and cognitive functions were tested yearly
- Tested rate of memory decline and for presence of dementia
- Outcomes:
  - E+P does not protect from normal decline
  - E+P showed increase in dementia

WHI Critiques

- Studied only one estrogen and one estrogen/progestin combination
- Women with moderate to severe menopausal symptoms discouraged
- QOL measurement tools geared to measure only chronic health conditions
- High drop-out rates: 42% E+P group, 39% placebo group

WHI Critiques II

- Narrow focus led to bias against areas of known HRT benefit:
  - Women with osteoporosis were excluded
  - Over 1200 women with previous cardiovascular events were included
  - No routine colonoscopy or bone density
- Global index was not validated

Mystique of Menopause III

- One is not born a woman, one becomes one.

  -Simone DeBeauvoir

- I refuse to think of them as chin hairs. I think of them as stray eyebrows.

  - Janette Barber

- If I had my life to live again, I'd make the same mistakes, only sooner.

  - Tallulah Bankhead

Recommendations for HRT

- The FDA Black Box
- Current labeling: Indications and usage
- USPSTF
- NAMS

The FDA Black Box

- Estrogens and progestins should not be used for the prevention of cardiovascular disease.

- Other doses of CEE and MPA and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar

Current Labeling

- Treatment of moderate to severe symptoms associated with menopause
- Treatment of moderate to severe symptoms associated with vaginal and vulvar atrophy assoc. with menopause
- Prevention of postmenopausal osteoporosis in women at significant risk, after considering non-hormonal rx

North American Menopause Society

www.menopause.org

NAMS
THE NORTH AMERICAN MENOPAUSE SOCIETY

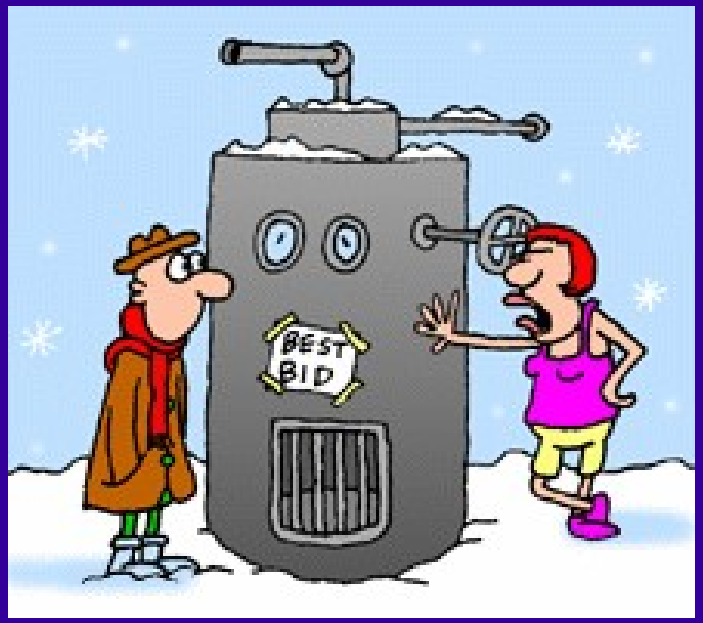
- Position Statement
  - Treatment of moderate and severe menopause symptoms remains the primary indication for systemic estrogen therapy (ET) and combined estrogen-progestogen therapy (EPT)
  - The primary menopause-related indication for progestogen use is endometrial protection from unopposed ET
  - No EPT regimen should be used to prevent CAD

USPSTF

- **U.S. Preventive Services Task Force** November 2002
  - **The USPSTF recommends against the routine use of E+P for the prevention of chronic conditions in postmenopausal women. D recommendation.**
  - **The USPSTF concludes that the evidence is insufficient to recommend for or against the use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. I recommendation**

HRT Alternatives

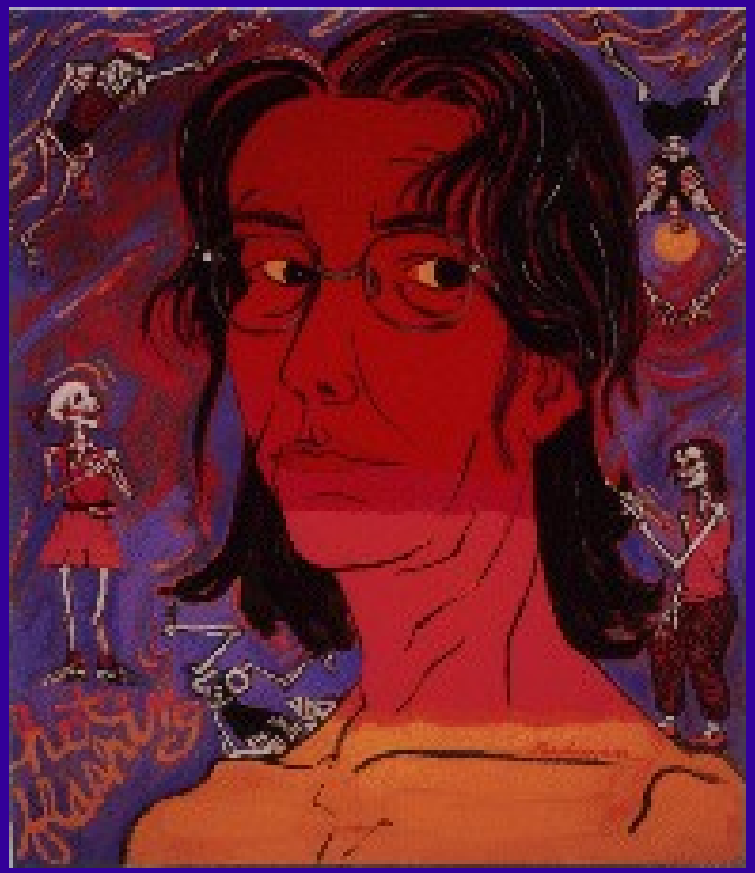
- General Interventions
- Vasomotor Symptoms
- Osteoporosis
- Urogenital Atrophy
- Mood Disorders
- Cardiovascular Disease



General Interventions

- Exercise
- Adequate vitamins D, K, and calcium
- Normalize BP, lipids, sugar, and weight
- Routine cancer screening
- Avoid tobacco, minimize Etoh

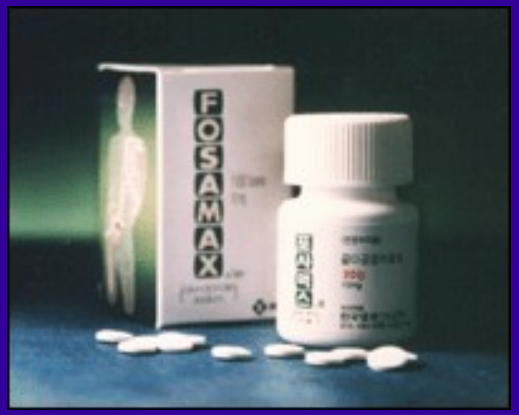
Vasomotor Symptoms



- Behavioral interventions
- Hormonal therapy
  - Low-dose 0.3mg CEE
  - BID of half dose if ineffective
- Non-hormonal therapy
- Isoflavones
  - 40 – 80 mg/day
- Other herbals
  - Black Cohosh: 20mg bid
  - Vit E: no proven benefit

Osteoporosis

- Prevention
  - Falls
  - Screening
  - Weight bearing
- Bisphosphonates
- SERMS
- PTH
- Calcitonin
- Estrogen



Non-modifiable fracture risk factors

- Advanced age
- Female gender
- Personal or family history of adult fracture
- Dementia
- Caucasian race
- Poor health or frailty*

Modifiable fracture risk factors:

- Low body mass (<127 pounds)
- Low lifelong calcium intake
- Substance use/ abuse
- Deconditioning
- Poor visual acuity
- Polypharmacy
- Excessive alcohol use
- Estrogen deficiency
  - Early menopause (<45)
  - Bilateral ovariectomy
  - Prolonged (>12 months) premenopausal amenorrhea
- Smoking

Cummings, *NEJM*, 1995; NOF, *Physician's guide*, 2000

Urogenital Atrophy

- Water based lubricants
- Vaginal moisturizers
  - Replens
  - Silken
- Topical estrogen
- Vaginal ring
- Soy foods
  - Improvement in vaginal dryness in one study (Brzenzski, 1997)

Mood Disorders

- Evaluate the whole patient and situation
- SSRIs are treatment of choice
- Beware of sexual side effects

Cardiovascular Disease

- Lifestyle measures
- Normalize
  - BP
  - Blood Glucose
  - Lipids
  - Body weight
- Smoking cessation
- Alcohol moderation

Summary

- HRT is not recommended for prevention of CAD
- HRT is approved for treatment of moderate to severe menopausal sx
- HRT is approved for osteoporosis prevention in certain patients
- For approved conditions HRT should be used in the low dose for short duration

Conclusions

- Never has it been more critical to be a teaching doctor
- Patient risk factors are key in choosing appropriate candidates for HRT
- In the final analysis the patient will chose what she feels is best for her

Helpful Websites

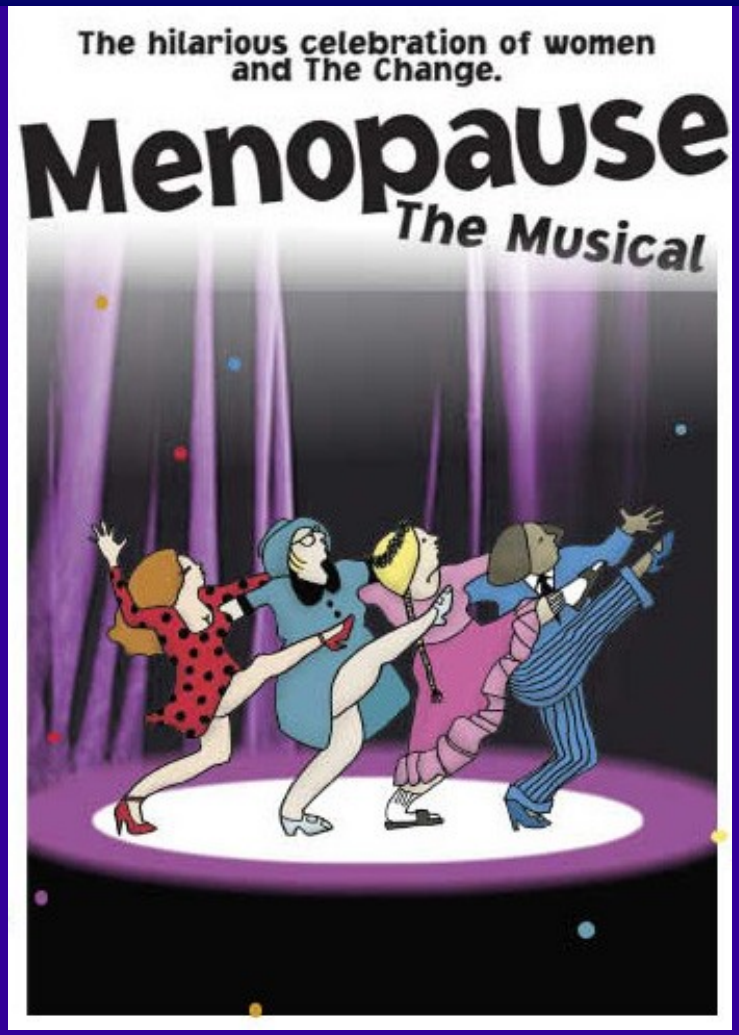
- www.menopause.org: NAMS
- http://www.cme.wisc.edu/online/menopause/sld001.htm : UW menopause review
- www.4women.gov/owh: DHHS Office of Women's Health
- www.nhlbi.**nih.gov/health/women/index.htm**: WHI website

Mystique of Menopause IV

"Ladies, I apologize for all of us. That men are genetically inferior is no secret. Count your blessings that we die off at a far younger age, leaving you the best part of your lives to appreciate the exquisite women you've become, without the distraction of some demanding old man clinging and whining his way into your serenity."

-Andy Rooney

Questions


The hilarious celebration of women and The Change.
Menopause
The Musical